REMARKS

The September 17, 2003 Official Action and the references cited therein have been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At page 2 of the Official Action, the Examiner has rejected claims 80 and 82 under 35 U.S.C. §112, first paragraph as allegedly failing to satisfy the written description and enablement requirements.

The Examiner has also considered the Declaration under 37 C.F.R. §1.131 and contends that it fails to overcome the Hu et al. reference. It is the Examiner's position that the Declaration fails to establish evidence of conception of a method for administering a PI-3 kinase inhibitor for treatment of aberrant angiogenesis earlier than the publication date of this reference.

Claim 80 remains rejected and new claim 89 stands rejected under 35 U.S.C. §102 as allegedly anticipated by Hu et al. as evidenced by Jiang et al. and Oikawa et al. In connection with this rejection, the Examiner asserts that "endothelial apoptosis is the same as inhibiting angiogenesis since apoptosis of endothelial cells involved would lead to inhibition of angiogenesis according to Shibuya et al." Applicant strenuously disagrees with the Examiner's position for the reasons set forth below.

Claim 82 is objected to under 37 C.F.R. §1.175c as allegedly being of improper dependent form.

At page 6 of the Official Action, the Examiner has rejected claims 80 and 82 under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

The Examiner has rejected claim 90 under 35 U.S.C. §103(a) as allegedly unpatentable over Hu et al. as applied to claim 80 and further in view of Oikawa et al.

Finally, the Examiner indicates that if the written description rejection of claim 82 were overcome, the claim would still be rejected under 37 C.F.R. §1.75 as a substantial duplicate of claim 80.

The foregoing constitutes the entirety of the objections and rejections raised in the September 17, 2003 Official Action. In light of the present claim amendments and the following remarks, each of the above-mentioned rejections under 35 U.S.C. §§112, first and second paragraph, 102 and 103 is respectfully traversed.

CLAIM 80 AS AMENDED FULLY SATISFIES THE WRITTEN DESCRIPTION REQUIREMENT

moot w/ proposed Amendment

The Examiner has rejected claims 80 and 82 as allegedly failing to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. Specifically, it is the Examiner's position that Applicant has not disclosed a sufficient number of compounds to justify the breadth of claim 80 and further that the specification allegedly fails to disclose a compound which functions as an AKT inhbitor. This rejection of the claims as amended cannot be maintained. As noted in the MPEP at § 2163,

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.
>
> Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention.

Clearly, the specification provides a thorough description of two different compounds that function in the

method as claimed and also provides a variety of protocols for identifying new compounds for treating tumor-induced aberrant angiogenesis. Accordingly, Applicant submits that specification as filed fully complies with the requirements of 35 U.S.C. §112, first paragraph. However, in the interest of expediting prosecution, Claim 80 has been amended to recite a Markush group consisting of LY294002 and wortmannin, thereby rendering the rejection of the claim for inadequate written description moot.

The Examiner further asserts that the subject matter encompassed by claim 82 was not adequately described because the specification does not describe a specific AKT inhibitor. The Examiner takes exception to Applicant's assertion that a PI3 kinase inhibitor can also be considered an AKT inhibitor because "it does not make sense to give two different names to a single entity". The Examiner is ignoring the scientific basis for this assertion. As shown in the specification, LY294002 inhibits AKT activity. It is also known that LY294002 inhibits PI3 kinase. If two enzymes function in a cascade-like fashion in a signal transduction pathway, it necessarily follows that in some instances a putative PI3 kinase inhibitor would also function as an AKT inhibitor and thus could be referred to interchangeably as an AKT inhibitor or a PI3 inhibitor. Referring to such a molecule in this way does make sense and is often done in the art. For example, staurosporine is a tyrosine kinase inhibitor which is also referred to as

The Examiner relies of Zhou et al. for the contention "that something that inhibits AKT does not necessarily inhibit PI-3" so they could not be the same. This statement is illogical. Asserting that a compound "does not necessarily inhibit two enzymes in a pathway does not rule out the possiblitity that another molecule could modulate the enzymatic activities of both enzymes. While strenuously

disagreeing with the Examiner's contention that claim 82 has not been adequately described, Applicant has amended the claim to recite that the inhibitor of claim 80 also inhibits AKT. Support for this amendment can be found throughout the specification and does not introduce new matter into the application. Accordingly, Applicant requests that the rejection of claim 82 as amended be withdrawn.

CLAIM 80 AS AMENDED IS NOT ANTICIPATED BY HU ET AL. AS EVIDENCED BY JIANG ET AL. OR OIKAWA ET AL.

The Examiner has maintained the rejection of claim 80 under 35 U.S.C. §102(a) as allegedly anticipated by Hu et al. as evidence by Jiang et al. or Oikawa et al. The Examiner has completely ignored the fact that Hu et al. are completely silent regarding the ability of LY294002 to affect "tumor induced aberrant angiogenesis". Indeed, the word angiogenesis does not appear in this reference. A careful review of Hu et al. reveals the following:

mechanism of action of the product ↓ inherent property

The LY294002 compound was effective to reduce tumor growth and ascites formation in a nude mouse model of ovarian cancer. Applicants again reiterate that ascites formation is not associated with aberrant angiogenesis. As reported by Hu et al., LY294002 dramatically inhibited OVCAR-3 cell proliferation directly (See Figure 4). Notably, OVCAR-3 cells are derived from epithelial cells. Thus, the compound is shown to exert demonstrable, toxic effects directly on the tumor cells themselves and the skilled person is left to wonder whether the molecule has any effect whatsoever on tumor-induced aberrant angiogenesis. Furthermore, Hu et al. do not even mention effects on angiogenesis in the proposed two mechanisms of action for the LY294002 compound. See page 884, first column. "One possibility is that LY294002 inhibits

cell cycle progression...The second possibility is that LY294002 increases apoptosis of ovarian carcinoma". To anticipate a claim, the reference must teach each and every element of the claim. It is indisputable that Hu et al. do NOT teach each and every element of claim 80.

The Examiner then relies upon Jiang et al. or Oikawa et al. as evidence that the method of claim 80 is anticipated by Hu et al. According to the MPEP §2131:

"To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such a gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill." Continental Can C. USA v. Monsanto Co., 20 U.S.P.Q. ed 1746, 1749 (Fed. Cir. 1991). Furthermore, as set forth in MPEP §2112, "The fact that a certain result or characteristic may occur or be present in the prior art is NOT sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 28 U.S.P.Q. 2d 1955, 1957 (Fed. Cir. 1993)...Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is NOT sufficient." In re Robertson, 49 U.S.P.Q.2d 1949, 1950-51, Fed. Cir. 1999).

Jiang et al. and Oikawa et al. describe experiments to assess angiogenesis in a "growing chick embryo chorioallantoic membrane assay". Accordingly, both of these references describe the effects of wortmannin and LY294002 on embryonic angiogenesis, a system which is completely unrelated to tumor formation. Indeed, embryonic angiogenesis is a natural, regulated process of cell signaling which results in maturation of the chick embryo.

Jiang et al. perturbed this artificial, *in vitro* system by overexpressing viral oncogenes in an avian retroviral vector in a constitutive fashion. It is this addition of the retroviral oncoproteins that resulted in aberrant angiogenesis. See Figures 1 and 2. Applicant submits that the skilled person, at the time the application was filed, would not view the in vitro systems of Jiang et al. and Oikawa et al. as "evidence" that in vivo administration of a PI3 or Akt kinase inhibitor would have a therapeutic effect on the aberrant angiogenesis observed in in situ tumors. Inasmuch as embryonic angiogenesis cannot be equated with angiogenesis that occurs during occult tumor formation, Applicant submits that the §102 rejection of claim 80 is improper and should be withdrawn.

Applicant further notes that in connection with the maintenance of this rejection in the final Official Action, the Examiner asserts the following:

"Applicant argues that Hu et al. do not teach the instant invention because administering a PI3 inhibitor to tumor-bearing mice by Hu et al. caused apoptosis, not inhibiting angiogenesis. *But this argument is not persuasive because endothelial cell apoptosis is same as inhibiting angiogenesis according to Shibuya, Cancer Sci. 2003.*"

At the outset, Applicant disagrees with the Examiner's sweeping statement that "endothelial cell apoptosis is the same as inhibiting angiogenesis". Certainly, there are certain circumstances where endothelial cell apoptosis has no effect whatsoever on angiogenesis. As indicated above, Hu et al. describe apoptosis of OVCAR-3 cells which are derived from epithelial cells as opposed to endothelial cells, thus Hu et al. certainly do NOT teach apoptosis of endothelial cells. Applicant has carefully reviewed Shibuya et al. which was published two years after Applicant's filing date. This

reference describes the structure, specific ligand and function of VEGFR-2. Furthermore, Applicant respectfully requests that the Examiner cite the passages in Shibuya to support the assertion that endothelial apoptosis is the same as inhibiting angiogenesis. Applicant have been unable to find this assertion in the reference. In light of the foregoing, it is submitted that the Examiner's reliance on this reference in support of the maintenance of the 102 rejection of claim 80 is misplaced and the rejection should be withdrawn.

THE AMENDMENT TO CLAIM 82 RENDERS THE OBJECTION TO THE CLAIM FOR IMPROPER DEPENDENCY MOOT AND ALSO SERVES TO CLARIFY THE METES AND BOUNDS OF THE CLAIM

Claim 82 has been amended to recite that the PI3 inhibitor of claim 80 also inhibits AKT. This amendment serves to further limit the subject matter of claim 80 and thereby is of proper dependent form. The Examiner has mischaracterized Applicant's statements submitted in the last response. Applicant has never asserted that all PI3 kinase inhibitors are also AKT inhibitors. As set forth above, a putative inhibitor could impact both PI-3 and AKT enzymatic activities and thus a single compound could be referred to interchangeably as an AKT inhibitor and a PI-3 kinase inhibitor. Claim 82 as amended encompasses the situation where the recited PI-3 kinase inhibitor also functions as an AKT inhibitor which is the case with the compound exemplified in the specification, LY294002. In light of the amendment to claim 82, Applicant submits that the metes and bounds of the claim are clear, the claim is of proper dependent form and is not a substantial duplicate of claim 80. Accordingly, Applicant requests that the rejection and objections to the claim be withdrawn.

THE SUBJECT MATTER ENCOMPASSED BY CLAIM 90 IS NOT OBVIOUS OVER HU ET AL. IN VIEW OF OIKAWA

The Examiner has rejected claim 90 under 35 U.S.C. §103 as allegedly obvious over Hu et al. in view of Oikawa et al. As discussed above, in connection with the rejection under §102, Hu et al. are silent regarding the anti-angiogenic effects of LY294002 and thus, do not disclose each and every element of the invention. Oikawa et al. were studying the effects of wortmannin on embryonal angiogenesis in a chick embryo system which does not mimic tumor formation in vivo. It is a well-settled premise in patent law that "silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow." In re Burt, 148 U.S.P.Q. 548 (CCPA 1966). Inasmuch as the disclosure in Oikawa et al. does not rectify the deficiencies of Hu et al., it cannot be reasonably maintained that the combination of these references renders the subject matter of claim 90 obvious.

Indeed, an article which appeared in Molecular Cancer Therapeutics in October 2002 by Bondar et al. (abstract attached) described the effects of administration of LY294002 and wortmannin on pancreatic cancer cells in an in vivo mouse model. These investigators reported on the apoptotic effects of these compounds. No mention whatsoever of the effects on angiogenesis are disclosed or suggested. Thus, the Examiner's assertion that the subject matter of claim 90 is obvious to the skilled person is not supported in the literature which was published two years after Applicant's filing date. Accordingly, Applicant requests that the rejection of claim 90 under 35 U.S.C. §103 be withdrawn.

CONCLUSION

No new matter has been introduced into this application by reason of any of the amendments presented herewith. Moreover, none of the present claim amendments is believed to constitute a surrender of any originally claimed subject matter, or a narrowing of the claims in order to establish patentability. The effect of these amendments is merely to make explicit that which was implicit in the claims as originally worded.

It is respectfully requested that the amendments presented herewith be entered in this application, since the amendments are primarily formal, rather than substantive in nature. This amendment is believed to clearly place the pending claims in condition for allowance. In any event, the claims as presently amended are believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case.

In view of the present claim amendments, and the foregoing remarks, it is respectfully urged that the rejections set forth in the September 17, 2003 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is

requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,
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